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(54) Title: MICRODISPERSE DRUG DELIVERY SYSTEMS

(57) Abstract

Methods and compositions relating to microdispersion formulations for enhanced bioavailability of therapeutic agents are disclosed. Microdispersions of the compositions of the invention are formed upon contact with aqueous fluids, including physiologic fluids.

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# MICRODISPERSE DRUG DELIVERY SYSTEMS

## Background of the Invention

The invention relates to a microdispersion system for enhancing the solubility and bioavailability of therapeutic agents.

Unlike hydrophilic compounds, the delivery of lipophilic therapeutic agents by conventional means has been and continues to be problematic. If solubility is low, incomplete and/or erratic absorption may result, with absorption being erratic on an intra-patient or inter-patient basis. The insolubility of large lipophilic particulates tends to reduce delivery rates because little therapeutic agent dissolves in the gastrointestinal liquid and crosses the epithelial barrier before it is excreted. Additionally, the degradation of labile therapeutic agents by gastric fluids may reduce therapeutic agent bioavailability to the point of therapeutic failure (Prescott, L.F., in *Novel Drug Delivery and its Therapeutic Application*, John Wiley & Sons, New York, 1989, pp. 3-4).

In spite of the difficulties associated with the delivery of lipophilic therapeutic agents, the potential advantages in developing methods for the delivery of such therapeutic agents is great. Extensive work has been done to show that the membrane permeability and efficacy of therapeutic agents often increases with increasing lipophilicity (Banker and Rhodes in *Modern Pharmaceutics*, Marcel Dekker, Inc., New York, 1979, pp. 31-49; Hughes and Mitra, 1993, *J. Ocul. Pharmac.* 9:299; Yokogawa et al., 1990, *Pharm. Res.* 7:691; Hageluken et al., 1994, *Biochem. Pharmac.* 47:1789). Therefore, the development of new systems for the delivery of lipophilic compounds could potentially increase the therapeutic efficacies for the treatment of a wide variety of indications.

## Summary of the Invention

In accordance with this invention, it has been discovered that enhanced bioavailability of therapeutic agents, particularly poorly soluble therapeutic agents, may be obtained using a microdispersion system. It has also been discovered that

greater sustained delivery of therapeutic agents may be achieved with the microdispersion system. The microdispersion system is characterized by the formation of a discontinuous phase of droplets when the pharmaceutical compositions of the invention contact an aqueous environment, particularly physiologic fluids. As used herein, droplets means any aggregate of the discontinuous phase, including for example, droplets, micelles or vesicles, including any of the above associated with particulate matter, such as for example, particles of a therapeutic agent. The formation of a microdispersion improves the absorption of the therapeutic agent from the aqueous environment, thereby enhancing the bioavailability of the therapeutic agent.

The methods and compositions of this invention are particularly applicable to the oral administration of therapeutic agents and the absorption of such agents in the gastro-intestinal tract. However, the methods and compositions of this invention may also be applicable to the administration of a therapeutic agents in other aqueous environments.

The pharmaceutical compositions of this invention comprise at least one therapeutic agent, a microdispersion formulation, and optionally, other excipients. The microdispersion formulation comprises a solid, semi-solid, or liquid mixture of a polyglycolyzed glycerides component, a polyoxypropylene-polyoxyethylene block copolymer component, ethanol, and optionally, other excipients.

The polyglycolyzed glycerides component of the microdispersion composition may include all grades of saturated and unsaturated polyglycolyzed glycerides, including but not limited to caprylocaproyl macroglycerides (commercially known as Labrasol®, Labrafac®, Hydro WL1219), Gelucire ® 44/13 and Gelucire ® 50/13 (available from Gattefosse). Preferred polyglycolyzed glycerides are those with a hydrophilic-lipophilic balance (HLB) greater than 10.

The microdispersion comprises a solid, semi-solid, or liquid form. In general, the presence of a larger percentage of caprylocaproyl macroglyceride in the composition permits the formulation of semi-solid and/or liquid forms. The respective grades of polyglycolized glycerides and, optionally, d-alpha-tocopheryl polyethylene glycol 1000 succinate are combined to produce a solid, semi-solid, or

liquid form. Commercial caprylocaproyl macroglycerides compositions have a defined combination of mono-, di-, and triglycerides and mono- and di- fatty acid esters of PEG. The caprylocaproyl macroglycerides compositions may comprise the following fatty acid chain lengths: C8, C10, C12, C14, C16, and C18, any of which may comprise 1-99% of the fatty acid components of the composition. Generally, the predominance of C8-C10 fatty acid chains in the composition yield liquid to semi-solid formulations. The predominance of C12-C14 fatty acid chains in the composition yields liquid, semi-solid, or solid formulations. The predominance of >C14 fatty acid chain lengths in the composition yields semi-solid or solid formulations. Therefore, the system can employ any combination of the above to achieve the desired solid, semi-solid, or liquid form.

The polyoxypropylene-polyoxyethylene block co-polymer component of the microdispersion composition may include all grades of polyoxypropylene-polyoxyethylene block co-polymer, preferably polyoxypropylene-polyoxyethylene block co-polymers with a HLB greater than 10. Preferred polyoxypropylene-polyoxyethylene block co-polymers include Pluronic® NF Surfactants, such as for example, Pluronic® L44, Pluronic® F68, Pluronic® F108, and Pluronic® F127 (available from BASF).

The components of the microdispersion formulation of the invention (polyglycolyzed glycerides/ polyoxypropylene-polyoxyethylene block co-polymer/ethanol) may be combined in virtually any weight ratio, including widely diverging weight ratios such as the following: (0.050/99.9/0.05) to (99.9/0.05/0.05) to (0.05/0.05/99.9). Preferable weight ratios of polyglycolyzed glycerides/ polyoxypropylene-polyoxyethylene block co-polymer/ethanol are the following: 8/0.5/1.5, 7/2/1, 6/3/1, 6/1/3, 5/4/1, 5/1/4, 4/3/3,4/4/2, 3/6/1 and 2/6/2. The weight ratios are preferably constituted to yield a mixture having a melting point in the range of about 20°C to about 70°C, preferably in the range of about 50°C to about 70°C. The microdispersion formulations, when employed as part of the pharmaceutical compositions of this invention, facilitate the formation of a microdispersion of droplets upon contact of the pharmaceutical compositions with an aqueous environment, including physiological fluid. The droplet diameter may vary

from about 0.05$\mu$ to about 1500$\mu$. Preferably, the droplets have an average diameter of less than about 500$\mu$ and more preferably, an average diameter of less than about 50$\mu$. A smaller diameter enhances bioavailability of the therapeutic agent.

The pharmaceutical compositions of this invention are characterized in that greater than 1% of the total therapeutic agent content exists in solution in the system, in either the solid, semi-solid, or liquid phases. The composition is also characterized in that a portion of the therapeutic agent can exist as a solid dispersion. Any portion of the therapeutic agent which exists as a solid dispersion preferably has a particle size distribution wherein the diameter of about 90% of the particles is less than 10$\mu$ (D90 < 10$\mu$). The solubilized therapeutic agent/dispersed therapeutic agent ratio is in a range from 1/99 to 100/0. Preferably, about 30% to about 100% of the therapeutic agent exists in solution, and more preferably, about 60% to about 100% of the therapeutic agent exists in solution. The ratio of the polyglycolyzed glycerides/polyoxypropylene polyoxyethylene block co-polymer is selected to facilitate solubilization of the therapeutic agent in the polyglycolyzed glycerides/polyoxypropylene polyoxyethylene block co-polymer system. The solubilized therapeutic agent/dispersed therapeutic agent ratio can be easily ascertained by the use of techniques in solution calorimetry that are well known in the art. The crystallinity of the therapeutic agent is easily determined by X-ray diffraction. The diameter of droplets of the microdispersion can be characterized by measuring any of droplet volume, droplet diameter, or droplet population, using techniques that are well known in the art. These techniques include for example, laser light scattering particle size analysis, coulter counter techniques, and freeze etching techniques.

The core component mixture of the microdispersion formulation (polyglycolyzed glycerides/polyoxypropylene polyoxyethylene block co-polymer/ethanol) may be present in the pharmaceutical composition in the range of from about 0.10 % to about 99.9%, preferably from about 5% to about 90%, and more preferably from about 30% to about 80%. The balance of the pharmaceutical composition is comprised of the therapeutic agent and excipients. The

polyglycolyzed glycerides component typically comprises about 1% to about 90% of the pharmaceutical composition, and preferably about 40% to about 80%. The polyoxypropylene polyoxyethylene block co-polymer component typically comprises about 1% to about 50% of the pharmaceutical composition, and preferably about 3% to about 35%. The ethanol component typically comprises about 1% to about 30% of the pharmaceutical composition, and preferably about 5% to about 15%.

Therapeutic agents that may be used in conjunction with this invention include any therapeutically active compounds. Therapeutic agents which have an intrinsic solubility in water of less than about 20.0 g/L, especially those with an intrinsic solubility of less than about 10.0 g/l, and/or therapeutic agents which have previously documented poor bioavailabilty are specifically contemplated as part of this invention. The therapeutic agent may be present in the pharmaceutical composition in the range of from about 0.10% to about 99.9%, preferably from about 5% to about 75%, and more preferably from about 30% to about 60%. Examples of therapeutic agents that may be used in conjunction with this invention include the following: dihydropyridine compounds, including for example, nifedepine, felodipine, nicardipine; cyclopeptides, including for example cyclosporin; paclitaxel, omperazole; spironolactone; furosemide; terbutaline; riboflavin; gemfibrozil; indomethacin; ibuprofen; phenytoin; and glyburide. Additionally, any therapeutic agent with an intrinsic solubility of less than about 10.0 g/L and having therapeutic activity in any of the following areas are contemplated as part of this invention: activity in the cardiovascular system; immunosuppressive activity; cholesterol lowering activity; anti-hypertensive activity; anti-epileptic activity; hormonal activity; hypoglycemic activity; anti-viral activity; anti-histaminic activity; nasal decongestant activity; anti-microbial activity; anti-arrthrytic activity; analgesic activity, anti-mycobacterial, anti-cancer activity, diuretic activity, anti-fungal activity, anti-parasitic activity, activity as a central nervous system (CNS) stimulant, activity as a CNS depressant, activity as a 5-HT inhibitor, anti-schizophrenia activity, anti-alzheimer activity, anti-psoriatic activity, anti-ulcer activity, activity as a proton pump inhibitor, anti-asthmatic activity, activity as a bronchodialator, and thrombolytic activity. The therapeutic agent may

be, for example, a protein, a peptide, a cyclopeptide, a steroid molecule, a vitamin, an oligonucleotide, or any small or large molecule, or any combination of the foregoing.

The pharmaceutical compositions and microdispersion formulations of this invention may comprise excipients. Excipients may be added to the pharmaceutical composition for a variety of reasons, including, for example, to accomplish the following purposes: increase the solubility of the therapeutic agent in the microdispersion composition; improve the chemical stability of the system; set the melting point of the system; alter or control or modify the release profile of the therapeutic agent from the pharmaceutical composition; enhance attributes useful for processing and formulation of the pharmaceutical composition, such as for example, flowability and direct compressibility. Excipients may comprise from about 5% to about 95% by weight of pharmaceutical composition, preferably from about 10% to about 70%.

Examples of suitable excipients that may be used in conjunction with this invention are the following: glycerol; glyceryl monooleate; glyceryl monosterate; glyceryl palmitosterate; triglycerides; diglycerides; monoglycerides; diesters of polyethylene glycol (PEG); monoesters of PEG; propylene glycol; glyceryl polyoxyethylene fatty acid esters; glyceryl polyoxyethylene polyethylene glycol fatty acid esters and ethers; polyoxyethylene alkyl ethers; polyoxyethylene castor oil derivatives; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene sterates; polyvinyl alcohol; sodium starch glycollate; sorbitan fatty acid esters; polyoxyl sterates; polyethylene glycol hydroxysterate; polyoxyethylene alcohols; anionic; cationic; amphiphilic compounds; lecithins; phospholipids; carbohydrates, including for example, lactose, maltodextrins, sucrose, and starch; polyols, including for example, sorbitol, mannitol, and xylitol; microcrystalline cellulose; vitamins, including for example, ascorbic acid and niacinamide; and inorganic compounds, including for example, calcium carbonate, dicalcium phosphate, and any combinations of the above mentioned materials.

A preferred excipient of the microdispersion formulation comprises water soluble tocopherol derivatives, preferably d-alpha-tocopherol polyethylene glycol

ester, and more preferably d-alpha-tocopheryl polyethylene glycol 1000 succinate. The water soluble tocopherol derivative preferably comprises about 1% to about 90% of the microdispersion formulation, and more preferably about 20% to about 60%. The preferable weight range of the tocopherol derivative in the final composition is about 10% to about 70%. Other tocopherol based excipients include ascorbyl palmitate and vitamin E acetate.

The invention also relates to a method for delivering one or more therapeutic agents to a physiologic target site. The method comprises the steps of providing a pharmaceutical composition according to the invention and introducing a pharmaceutically effective amount of the pharmaceutical composition to a physiologic target site. The pharmaceutical composition forms a microdispersion upon contact with physiologic fluids at the physiologic target site. The introduction of the pharmaceutical composition to the physiologic target site may be accomplished, for example, by administration topically, subcutaneously, intramuscularly, intraperitoneally, nasally, pulmonarily, vaginally, rectally, aurally, orally or ocularly. A preferred method for delivering at least one therapeutic agent to a physiologic target site that is contemplated by this invention is through oral delivery.

The invention also relates to methods of formulating a therapeutic agent. The method comprises providing the components of a microdispersion composition, including polyglycolyzed glycerides, polyoxypropylene-polyoxyethylene block copolymers, and ethanol, and mixing the components of the microdispersion composition with a therapeutic agent to form a pharmaceutical composition, wherein greater than 1% of the therapeutic agent is solubilized.

An example of a method of formulating a pharmaceutical composition of the invention is as follows. The polyglycolyzed glyceride component and the polyoxypropylene-polyoxyethylene block co-polymer component are heated until the mixture is melted. The therapeutic agent, which has been milled or micronized to a particle size range wherein D90 is less than 10 microns, is gradually added to the molten mixture with vigorous stirring while the mixture is maintained in a molten

state with sufficient temperature. Anhydrous ethanol is then added to the mixture with stirring.

Two alternative next steps include the following: (1) the temperature of the mixture is cooled to room temperature, the composition is then homogenized, if required, and other excipients may then be added to the mixture; and (2) if permitted by the nature of the therapeutic agent, the temperature of the mixture is maintained at 20°C above the melting point of the mixture, with constant stirring to ensure homogeneity of the mixture.

After all the ingredients are mixed, the formulation may be a liquid or it may be congealed to a solid or semi-solid mass. The formulation may be spray congealed in a spray drier or a fluidized bed drier to a powder. The formulation may also be congealed onto an excipient in a spray drier, a fluidized bed drier, a rotor mixer, a high shear granulator, a planetary mixer, a blender, or any conventional food and pharmaceutical processing equipment.

The compositions of the invention may be formulated in conventional, specialized, or novel pharmaceutical dosage forms including, for example, tablets, capsules, powders for inhalation, suppositories, suspensions and emulsions. The compositions of the invention may be congealed onto a solid pharmaceutical dosage form such as a tablet, capsule, and/or granule.

The entire disclosure of all patents, patent applications, and publications cited herein are hereby incorporated by reference. Particularly, U.S. Provisional Patent Application Serial No. 60/063,338, U.S. Patent Application Serial No. 09/050,913, U.S. Provisional Patent Application Serial No. 60/080,163, U.S. Provisional Patent Application Serial No. 60/085,417, U.S. Provisional Patent Application Serial No. 60/088,855, PCT Application PCT/ US 99/13223, U.S. Provisional Patent Application Serial No. 60/092,767 are hereby incorporated by reference.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely

illustrative, and not limitative, of the remainder of the disclosure in any way whatsoever.

In the following examples, all parts and percentages are by weight unless otherwise indicated.

## EXAMPLES

Example 1 - Manufacturing Method:

Caprylocaproyl macrogolglyceride (commercially known as Labrasol®, Labrafac®, or Hydro WL1219) and/or Lauroyl macrogolglycerides (commercially known as Gelucire® 44/14 or Labrafil® M2130CS), d-alpha-tocopheryl polyethylene glycol 1000 succinate, and polyoxypropylene-polyoxyethylene block co-polymer (L44, which is a liquid) are heated to melt the mixture. The therapeutic agent is gradually added to the molten mixture with vigorous stirring, with maintenance of the system at a sufficiently high temperature to keep the mixture in a molten state. It is preferable that the therapeutic agent is milled or micronized to a particle size range such that D90 is < 10 microns. Anhydrous ethanol is then added to the mixture with stirring. The ratio of the polyglycolyzed glycerides: polyoxypropylene-polyoxyethylene block co-polymer : anhydrous ethanol is selected to facilitate solubilization of > 1% of the therapeutic agent, and preferably 30-100% of the therapeutic agent, in the polyglycolyzed glycerides/polyoxypropylene-polyoxyethylene block co-polymer/anhydrous ethanol system.

Two alternative next steps include the following: (1) the temperature of the mixture is cooled to room temperature, the composition is then homogenized, if required, and other excipients may then be added to the mixture; and (2) if permitted by the nature of the therapeutic agent, the temperature of the mixture is maintained at 20°C above the melting point of the mixture, with constant stirring during the addition of excipients to ensure homogeneity of the mixture. Excipients may be added to the microdispersion formulation or the pharmaceutical composition for many different purposes, including the following: increase the solubility of the

therapeutic agent; improve the chemical stability of the system; set the melting point of the system; alter/control/modify the release profile of the therapeutic agent; provide attributes such as flowability, direct compressibility, and other attributes desirable for processing and formulation of a dosage form.

After all the ingredients are mixed, the formulation may be a liquid or it may be congealed to a solid or semi-solid mass. The formulation may be spray congealed in a spray drier or a fluidized bed drier to a powder. The formulation may also be congealed onto an excipient in a spray drier, a fluidized bed drier, a rotor mixer, a high shear granulator, a planetary mixer, a blender, or any conventional food and pharmaceutical processing equipment.

The compositions of the invention may be formulated in conventional, specialized, or novel pharmaceutical dosage forms including, for example, tablets, capsules, powders for inhalation, suppositories, suspensions and emulsions. The compositions of the invention may be congealed onto a solid pharmaceutical dosage form such as a tablet, capsule, and/or granule.

Example 2 - Cyclosporin A Formulation (Dose: 100 mg/ml)

| Ingredients | Quantity (100 mls) | Quantity (1 liter) |
|---|---|---|
| Cyclosporin | 10.0 g | 100.0 g |
| Vitamin E TPGS | 10 ml | 100 ml |
| Labrasol | 65 ml | 65 ml |
| Pluronic L44 | 5 ml | 50 ml |
| Anhydrous ethanol | 10 ml | 100 ml |
| PEG-200 | 10 ml | 100 ml |
| Vitamin E acetate | 0.1 ml | 1.0 ml |
| Ascorbyl palmitate | 0.1 g | 1.0 g |

Manufacturing Procedure:

(1) Set the water bath to a temperature of 70 ± 2°C; (2) Melt Vitamin E TPGS and measure out 100 ml into a suitable container; (3) Stir the melted Vitamin E TPGS for 2 minutes using a mechanical stirrer at low speed; (4) Add 650 ml of Labrasol to

the Vitamin E TPGS, with continuous stirring; (5) Add 50 ml of Pluronic L-44 to the mixture, with stirring; (6) Stir the mixture for 30 minutes to ensure complete mixing of all the contents; (7) Reduce the temperature of the mixture to 50 ± 2°C and allow sufficient time to stabilize the temperature of the mixture at 50 ± 2°C; (10) Provide 100 g of Cyclosporin Ph. Eur; (8) With continuous stirring, slowly add the cyclosporin to the mixture over a period of 30 minutes (NOTE: Cyclosporin is a fine powder and is liable to clump); (9) Adjust the speed of the stirrer as necessary to obtain a uniform dispersion of cyclosporin in the mixture; (10) Maintain the temperature at 50 ± 2°C and continue stirring the contents for 1 hour; (11) Turn off the heat source on the water bath; (12) Increase the speed of the stirrer until a vortex is formed in the solution; (13) Rapidly add 100 ml of anhydrous alcohol to the vortex while continuing to stir; (14) Add 100 ml of PEG-200 to the mixture, with continuous stirring; (15) Add 1.0 ml of Vitamin E acetate to the mixture, with continuous stirring; (16) Add 1.0 gram of Ascorbyl Palmitate to the mixture, with continuous stirring; (17) Add Ascorbyl palmitate to the mixture and continue to stir for 15 minutes; (18) Turn off the stirrer; (19) Cover the container to prevent any further loss of alcohol and allow the mixture to cool down to room temperature; (20) Filter the mixture through a # 60 mesh screen to remove any extraneous particles; (21) The solution should be clear with no undissolved particles after filtering (NOTE: Air bubbles may be present in the solution and they should not be mistaken for undissolved particles).

Example 3 - Astemizole Formulation (Dose: 10 mg/ml)

| Ingredients | Quantity (100 ml) |
|---|---|
| Astemizole | 1.0 grams |
| Vitamin E TPGS | 5 ml |
| Labrasol | 50 ml |
| Pluronic L44 | 15 ml |
| Anhydrous ethanol | 10 ml |
| PEG-200 | 20 ml |
| Vitamin E acetate | 0.1 ml |

| | |
|---|---|
| Ascorbyl palmitate | 0.1 grams |

The Astemizole composition was prepared essentially according to the procedures described for the preparation of a cyclosporin composition in Example 2.

Example 4 - Azathioprine Formulation (Dose: 100 mg/ml)

| Ingredients | Quantity (100 ml) |
|---|---|
| Azathioprine | 10.0 grams |
| Labrasol | 75 ml |
| Pluronic L 44 | 15 ml |
| PEG-200 | 10 ml |
| Vitamin E acetate | 0.1 ml |
| Ascorbyl palmitate | 0.1 grams |

The Azathioprine composition was prepared essentially according to the procedures described for the preparation of a cyclosporin composition in Example 2.

Example 5 - Loratidine Formulation (Dose: 10 mg/ml)

| Ingredients | Quantity (100 ml) |
|---|---|
| Loratidine | 1.0 grams |
| Labrasol | 55 ml |
| Pluronic L44 | 20 ml |
| Anhydrous ethanol | 15 ml |
| PEG-200 | 10 ml |
| Vitamin E acetate | 0.1 ml |
| Ascorbyl palmitate | 0.1 grams |

The Loratidine composition was prepared essentially according to the procedures described for the preparation of a cyclosporin composition in Example 2.

Example 6 - Griseofulvin Formulation (Dose: 165 mg/ml)

| Ingredients | Quantity (100 ml) |
|---|---|
| Griseofulvin | 16.5 grams |
| Vitamin E TPGS | 10 ml |

| | |
|---|---|
| Labrasol | 60 ml |
| Pluronic L 44 | 10 ml |
| PEG-200 | 20 ml |
| Vitamin E acetate | 0.1 ml |
| Ascorbyl palmitate | 0.1 grams |

The Griseofulvin composition was prepared essentially according to the procedures described for the preparation of a cyclosporin composition in Example 2.

Example 7 - Diclofenac Formulation (Dose: 50 mg/ml)

| Ingredients | Quantity (100 ml) |
|---|---|
| Diclofenac | 5.0 grams |
| Vitamin E TPGS | 10 ml |
| Labrasol | 30 ml |
| Pluronic L44 | 30 ml |
| Anhydrous alcohol | 10 ml |
| PEG-200 | 20 ml |
| Vitamin E acetate | 0.1 ml |
| Ascorbyl palmitate | 0.1 grams |

The Diclofenac composition was prepared essentially according to the procedures described for the preparation of a cyclosporin composition in Example 2.

Example 8 - Minoxidil Formulation (Dose: 10 mg/ml)

| Ingredients | Quantity (100 ml) |
|---|---|
| Minoxidil | 1.0 grams |
| Labrasol | 55 ml |
| Pluronic L 44 | 15 ml |
| Gelucire( 44/13 | q.s. |
| Anhydrous ethanol | 10 ml |
| Propylene glycol | 10 ml |
| Vitamin E acetate | 0.1 ml |
| Ascorbyl palmitate | 0.1 grams |

The Minoxidil composition was prepared essentially according to the procedures described for the preparation of a cyclosporin composition in Example 2.

Example 9- Mitomycin C Formulation (Dose: 20 mg/ml)

| Ingredients | Quantity (100 ml) |
|---|---|
| Mitomycin | 2.0 grams |
| Labrasol | 60 ml |
| Pluronic L 44 | 15 ml |
| Anhydrous ethanol | 15 ml |
| PEG-200 | 10 ml |
| Vitamin E acetate | 0.1 ml |
| Ascorbyl palmitate | 0.1 grams |

The Mitomycin C composition was prepared essentially according to the procedures described for the preparation of a cyclosporin composition in Example 2.

Example 10 - Phenytoin Formulation (Dose: 50 mg/ml)

| Ingredients | Quantity (100 ml) |
|---|---|
| Phenytoin | 5.0 grams |
| Vitamin E TPGS | 10 ml |
| Labrasol | 50 ml |
| Pluronic L 44 | 10 ml |
| Anhydrous ethanol | 20 ml |
| PEG-200 | 10 ml |
| Vitamin E acetate | 0.1 ml |
| Ascorbyl palmitate | 0.1 grams |

The Phenytoin composition was prepared essentially according to the procedures described for the preparation of a cyclosporin composition in Example 2.

Example 11 - Paclitaxel Formulation (Dose: 6 mg/ml)

| Ingredients | Quantity (100 ml) |
|---|---|
| Paclitaxel | 0 600 grams |

| | |
|---|---|
| Vitamin E TPGS | 10 ml |
| Labrasol | 50 ml |
| Pluronic L 44 | 15 ml |
| Anhydrous ethanol | 15 ml |
| PEG-200 | 10 ml |
| Vitamin E acetate | 0.1 ml |
| Ascorbyl palmitate | 0.1 grams |

The Paclitaxel composition was prepared essentially according to the procedures described for the preparation of a cyclosporin composition in Example 2.

Example 12 - Tamoxifen Formulation (Dose: 10 mg/ml)

| Ingredients | Quantity (100 ml) |
|---|---|
| Tamoxifen | 1.0 grams |
| Vitamin E TPGS | 5 ml |
| Labrasol | 55 ml |
| Pluronic L 44 | 10 ml |
| Anhydrous ethanol | 20 ml |
| PEG-200 | 10 ml |
| Vitamin E acetate | 0.2 ml |
| Ascorbyl palmitate | 0.2 grams |

The tamoxifen composition was prepared essentially according to the procedures described for the preparation of a cyclosporin composition in Example 2.

Example 13 - Evaluation of oral Bio-availability:

The bio-availability of cyclosporin A in the preparation described in Example 2 above (the test preparation) was compared with the bioavailability of cyclosporin A in the commercial product Neoral (the control preparation). Both the test preparation and the control preparation were administered to six male New Zealand white rabbits,

and 2.5 ml blood samples were drawn from the marginal ear vein of the rabbits at the following pre- and post- dose times:

-5, 15, 30, 60, 120, 180, 240, 360, 480 minutes, and 24 hours.

The test preparation and the control preparation was administered orally at a dose of 100 mg/Kg after the animals had fasted overnight. The dose was delivered through tubing that had not been pre-saturated with the dosing solution. The dosing solutions were diluted approximately 1:2 with water. The control animals received 306 mg of the control preparation (32 mg of cyclosporin A) and the test animals received 247 mg of the test preparation (29 mg of cyclosporin A). Blood samples were analyzed by organic extraction, and then by HPLC analysis employing a modification of the method developed by Sawchuck et al, *Clin. Chem.* 1981; 27, # 8. The separation of cyclosporin A was carried out on a 150 mm x 4.6 mm I.D., Phenomenex Luna C18, reversed phase column. The column was maintained at 70°C and the detector was set at 210 nm. The mobile phase was 70% acetonitrile, and 30% water, brought to a pH of 3.1 by the addition of 1M phosphoric acid. The sample run time was 35 minutes.

The area under the blood concentration-time curve (AUC) for control animals was 590,195±111 (484 ng-min/ml). The maximum concentration (Cmax) of 1745±320 ng/ml was reached at 144±30 min (Tmax). The area under the blood concentration-time curve (AUC) for test animals was 606,253±177 (753 ng-min/ml). The maximum concentration (Cmax) of 821± 212 ng/ml was reached at 144±36 min (Tmax). The relative oral bioavailability of cyclosporin A in the microdisperse system versus the Neoral system was 1.27, indicating a 27% greater bioavailability of cyclosporin A using the microdisperse system.

Although the Cmax of cyclosporin A was higher in the control animals than in the test animals, the microdispersion system employed in the test animals appears to generate a broader concentration time profile in the absorption and the post-absorption phase. In the terminal phase, at least up to 24 hours, the cyclosporin A levels appear to be higher in the test animals that in the control animals. The 24 hour blood concentrations of cyclosporin A in the test animals was 198±60 ng/ml, compared to 117.7±76.1 ng/ml in the control animals. Therefore, in addition to enhanced oral

bioavailability of the cyclosporin A, the microdispersion system of the invention provided a more sustained delivery of cyclosporin A.

Example 14 - Cyclosporin A Composition

| | |
|---|---|
| cyclosporin A | 100 mg |
| dehydrated ethanol (U.S.P.) | 0.095 ml |
| Pluronic ® F127 | 0.25 g |
| Gelucire ® 4413 | 0.40 g |
| Vitamin E acetate | 0.0025 g |
| ascorbyl palmitate | 0.0025 g |
| propylene glycol | 0.25 g |

The above formulation is produced by first admixing the Pluronic® F127 and Gelucire ® 4413 at about 38-40°C. The Vitamin E acetate and ascorbyl palmitate are added at about the same temperature. Thereafter, the cyclosporin A is incrementally added under sufficient agitation to dissolve or uniformly disperse the therapeutic agent. The other ingredients are then added. The resultant liquid can be used as a liquid or it can be encapsulated, for example, in gelatin capsules.

Example 15 - Cyclosporin A Composition

| | |
|---|---|
| cyclosporin A | 200 mg |
| dehydrated ethanol (U.S.P.) | 0.08 g |
| Pluronic ® L44 | 0.207 g |
| Gelucire ® 44/14 | 0.312 g |

The Gelucire is melted and mixed with the Pluronic. The cyclosporin A is added to the mixture and dissolved in the mixture using heat. Ethanol is then added to the mixture. The resulting mixture was a clear solution, of low viscosity, even after cooling to room temperature.

Example 16 - Cyclosporin A Composition

| | |
|---|---|
| cyclosporin A | 400 mg |
| dehydrated ethanol (U.S.P.) | 0.16 g |
| Pluronic ® L44 | 0.414 g |
| Gelucire ® 44/14 | 0.624 g |

The Gelucire was dissolved into the Pluronic with slight heating, and ethanol was added to the mixture. The cyclosporin A was added to the above solution, while the temperature of the mixture is maintained at a temperature less than 40°C. Cyclosporin A dissolved in the mixture of ethanol, Gelucire, and Pluronic, although in some instances a small portion of the cyclosporin A was in the form of a sticky mass. The sticky mass started to dissolve with stirring and slight heat. The sticky mass could be prevented if the cyclosporin A was added to the mixture in small portions while stirring.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

**WHAT IS CLAIMED IS:**

1. A microdispersion formulation for use as part of a pharmaceutical composition comprising
(a) a polyglycolized glycerides component;
(b) a polyoxypropylene-polyoxyethylene block copolymer component; and
(c) ethanol.

2. A pharmaceutical composition comprising a microdispersion formulation according to claim 1 and at least one therapeutic agent.

3. A pharmaceutical composition according to claim 2, wherein at least one therapeutic agent has a solubility in water of less than 20.0 g/L.

4. A formulation according to claim 1, wherein either the polyglycolyzed glycerides component or the polyoxypropylene-polyoxyethylene block copolymer component has a hydrophilic-lipophilic balance of greater than 10.

5. A pharmaceutical composition according to claim 2, wherein the pharmaceutical composition forms a microdispersion upon contact with an aqueous environment, and wherein the droplets of the microdispersion have an average diameter of less than 500$\mu$.

6. A pharmaceutical composition according to claim 2, wherein 30% to 100% of at least one therapeutic agent is solubilized.

7. A microdispersion formulation according to claim 1, wherein the mixture of the polyglycolyzed glycerides component, the polyoxypropylene-polyoxyethylene block copolymer component, and the ethanol comprises from 5% to 75% of the microdispersion formulation.

8. A pharmaceutical composition according to claim 2, wherein the mixture of the polyglycolyzed glycerides component, the polyoxypropylene-polyoxyethylene block copolymer component, and the ethanol comprises from 5% to 75% of the pharmaceutical composition.

9. A pharmaceutical composition according to claim 2, wherein the therapeutic agent comprises from 5% to 75% of the pharmaceutical composition.

10. A microdispersion formulation according to claim 1, further comprising at least one water soluble tocopherol derivative.

11. A microdispersion formulation according to claim 10, wherein at least one water soluble tocopherol derivative is d-alpha-tocopheryl polyethylene glycol 1000 succinate.

12. A pharmaceutical composition according to claim 2, further comprising at least one water soluble tocopherol derivative.

13. A pharmaceutical composition according to claim 12, wherein at least one water soluble tocopherol derivative is d-alpha-tocopheryl polyethylene glycol 1000 succinate.

14. A pharmaceutical composition according to claim 2, wherein the therapeutic agent has an intrinsic solubility in water of less than 20.0 g/L.

15. A method of delivering at least one therapeutic agent to a physiologic target site comprising the steps of:

providing a pharmaceutical composition according to claim 2; and

introducing a pharmaceutically effective amount of the pharmaceutical composition to a physiologic target site, wherein the pharmaceutical composition forms a microdispersion upon contact with physiologic fluids at the target site.

16. A method according to claim 15, wherein the physiologic target site is the gastro-intestinal tract.

17. A method of delivering at least one therapeutic agent to a physiologic target site comprising the steps of:

providing a pharmaceutical composition according to claim 2; and

introducing a pharmaceutically effective amount of the pharmaceutical composition to a physiologic target site, wherein the pharmaceutical composition forms a microdispersion upon contact with physiologic fluids at the target site.

18. A method according to claim 17, wherein the physiologic target site is the gastro-intestinal tract.

19. A method of delivering at least one therapeutic agent to a physiologic target site comprising the steps of:

providing a pharmaceutical composition according to claim 3; and

introducing a pharmaceutically effective amount of the pharmaceutical composition to a physiologic target site, wherein the pharmaceutical composition forms a microdispersion upon contact with physiologic fluids at the target site.

20. A method according to claim 19, wherein the physiologic target site is the gastro-intestinal tract.

21. A method of delivering at least one therapeutic agent to a physiologic target site comprising the steps of:

providing a pharmaceutical composition according to claim 1; and

introducing a pharmaceutically effective amount of the pharmaceutical composition to a physiologic target site, wherein the pharmaceutical composition forms a microdispersion upon contact with physiologic fluids at the target site, and wherein the droplets of the microdispersion have an average diameter of less than 500$\mu$.

22. A method according to claim 21, wherein the physiologic target site is the gastro-intestinal tract.

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(57) Abstract

Methods and compositions relating to microdispersion formulations for enhanced bioavailability of therapeutic agents are disclosed. Microdispersions of the compositions of the invention are formed upon contact with aqueous fluids, including physiologic fluids.

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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

none

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 5,565,188 A (WONG et al) 15 October 1996, col. 1, lines 65-67; col. 2, lines 1-9,59 ; col. 4, lines 18-67; col. 5 lines 1-30; col. 7, lines 22-67; col. 10, lines 1-16; col. 11, lines 4-6; col. 12, lines 25-30; col. 13, lines 5-8. | 1-22 |

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